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Effect of *Gongjindon* a Traditional Korean Polyherbal Formula, on the Pharmacokinetics Profiles of Donepezil in Male SDRats (1)

-*Single Oral Combination Treatment of Donepezil 10mg/kg with Gongjindan 100mg/kg within 5 min*-

Dae-Kyoo Chung,[1] Oh-Dae Kwon,[2] Soo-Jin Park,[3,5]
Young-Joon Lee,[4,5]* Sae-Kwang Ku[3,5]*

[1]Department of Neuropsychiatry, College of Korean Medicine, DaeguHaany University, Gyeongsan
[2]Department of Neurology, Catholic University of Daegu School of Medicine, Daegu
[3]Department of Anatomy and Histology, College of Korean Medicine, DaeguHaany University, Gyeongsan
[4]Department of Preventive Medicine, College of Korean Medicine, DaeguHaany University, Gyeongsan
[5]The Medical Research center for Globalization of Herbal Formulation, DaeguHaany University, Gyeongsan

Abstract

Objectives : This study was aim to evaluate effects of pharmacodynamics and toxicity in combination therapy of donepezil with *Gongjindan*.

Methods : After 10mg/kg of donepezil treatment, *Gongjindan* 100mg/kg was administered within 5 min. The plasma were collected at 30min before administration, 30min, 1, 2, 3, 4, 6, 8 and 24hrs after end of *Gongjindan* treatment, and plasma concentrations of donepezil were analyzed using LC-MS/MS methods. PK parameters of donepezil were analysis as compared with donepezil single administered rats.

Results : *Gongjindan* markedly inhibited the absorption of donepezil regardless of sample time, from 30min to 8hrs after end of co-administration comparing with donepezil single treated rats. Especially the absorption of donepezil was significantly decreased at 2hrs after co-administration as compared with donepezil single treated rats, in the present study. Accordingly, the Cmax(-27.76%), AUC_{0-t}(-27.22%) and AUC_{0-inf}(-26.54%) of donepezil in co-administered rats were significantly decreased as compared with donepezil single treated rats, respectively.

Conclusions : Based on the results of the present study, co-administration of *Gongjindan* decreases the

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* 공동교신저자 : 이영준, 대구한의대학교 한의과대학 예방의학교실, 경북 경산시 한의대로 1, 712-715
전화 : 053-819-1296, 팩스 : 053-819-1576, 전자우편 : gksxntk@dhu.ac.kr
구세광, 대구한의대학교 한의과대학 해부학교실, 경북 경산시 한의대로 1, 712-715
전화 : 053-819-1549, 팩스 : 053-819-1576, 전자우편 : gucci200@hanmail.net

oral bioavailability of donepezil by inhibiting the absorption. It is considered that the more detail pharmacokinetic studies should betested to conclude the effects of *Gongjindan* on the pharmacokinetics of donepezil, when they were co-administered, like the effects after co-administration with reasonable intervals considering the Tmax of donepezil and after repeated co-administrations.

Key words : *Gongjindan*, Pharmacokinetics, Drug-drug interactions, Rat, Donepezil

I. Introduction

Donepezil (Aricept^{TM}) is a centrally acting reversible acetylcholinesterase inhibitor, and main therapeutic use is in the palliative treatment of mild to moderate Alzheimer's disease[1]. Donepezil is indicated for symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type[2, 3]. Donepezil has been tested in other cognitive disorders including Lewy body dementia[4] and vascular dementia[5]. Donepezil has also been found to improve sleep apnea in Alzheimer's patients[6], and recently the evidence that donepezil can improve speech in children with autism was also suggested[7, 8]. However, it also showed severe toxicity in preclinical studies, 50% lethal dose (LD_{50}) in rodents are located between 30~40mg/kg, and No Observed Effect Level(NOEL) of 13 weeks repeat dose toxicity test in rat and dog is 1mg/kg/day, respectively[9] and undesirable side effects in clinical use[10]. Common side effects include gastrointestinal upset; include bradycardia, nausea, diarrhea, anorexia, abdominal pain, vivid dreams, and mania[11-13].

As results of combination therapies with other drugs to improve the side effects of donepezil or to achieve synergic effects, various drug-drug interactions of donepezil have been evaluated ; Although, pharmacokinetic studies showed no significant effects of donepezil on the pharmacokinetic profiles of cimetidine[14], combinations containing any of the following medications, depending on the amount present, may also interact with anticholinergics - cholinesterase inhibitors such as donepezil have the potential to interfere with the activity of these medications, nonsteroidal anti-inflammatory drugs (NSAIDs) - donepezil may increase gastric acid secretion due to increased cholinergic activity; patients should be monitored for symptoms of active or occult gastrointestinal bleeding and carbamazepine, dexamethasone, phenobarbital, phenytoin or rifampin - They may induce the isoenzymes CYP2D6 and CYP3A4, thus increasing the rate of elimination of donepezil[9]. In addition, concurrent use of cholinergic agonists like bethanechol or neuromuscular blocking agents metabolized by plasma cholinesterase like succinylcholine and mivacurium with donepezil may be expected with a synergistic effect[9]. Ketoconazole also can be influenced on the pharmacokinetics and pharmacodynamics of donepezil through inhibition of the metabolism of donepezil[9), 15]. Interactions with herbal products have not been established except for some restricted

single herb extracts or natural compounds; *Ginkgo biloba* extracts[16], digoxin[17], theophylline[18], or warfarin[19], did not influence on the pharmacokinetics of donepezil.

Gongjindan, a traditional Korean polyherbal formula is one of the most famous tonic agents, and consisted of 4 herbs including *Angelicaegigas* radix, Ginseng steamed red, *Cornifructus* and *Rehmanniae* radix preparata, and 2 animal resources - antler and musk. These 6 agents were plastered using honey, and coated by gold plates. The hypolipidemicand immune stimulatory effects of *Gongjindan* are relatively well documented[20, 21] with anti-oxidative effects[22], anti-gliosis effects on middle cerebral artery occlusion rats[23] and anti-dementia effects[24, 25]. In addition, single oral dose toxicity[26] and micronucleus test[27] of *Gongjindan* itself were already reported.

In the present study, the effects of *Gongjindan* co-administration on the pharmacokinetics of donepezil were observed as a process of the comprehensive and integrative medicine, combination therapy of donepezil with *Gongjindan* to achieve synergic pharmacodynamics and reduce toxicity. After 10mg/kg of donepezil treatment, *Gongjindan* 100mg/kg was administered within 5 min. The plasma were collected at 30min before administration, 30min, 1, 2, 3, 4, 6, 8 and 24hrs after end of *Gongjindan* treatment, and plasma concentrations of donepezil were analyzed using LC-MS/MS methods. PK parameters of donepezil (Tmax, Cmax, AUC, $t_{1/2}$ and MRT_{inf}) were analysis as compared with donepezil single administered.

II. Materials and Methods

1. Animals and husbandry

Total tenmale Sprague-Dawley (SD)rats (6-wk old upon receipt, SLC, Japan) were used after acclimatization for 16 days. Animals were allocated five per polycarbonate cage in a temperature (20-25℃) and humidity (40-45%) controlled room. Light : dark cycle was 12hr : 12hr and feed (Samyang, Korea) and water were supplied free to access. All animals were marked by picric acid, and overnight fasted (about 18 hrs; water was not restricted) before treatment, and further fasted during 3 hrs after end of treatment.

2. Test articles and formulation

Gongjindan, prepared and purchase from Daegu Oriental Hospitals, DaeguHaany University (Table 1; Daegu, Korea) and donepezil(Jeil Pharm., Co., Ltd, Youngin, Korea) was used as control drug. Donepezil and Gongjindan were stored in a refrigerator at 4℃ to protect from light and degeneration until use. Both drugs are well suspended or dissolved (up to 20 mg/ml suspensions in Gongjindan and up to2mg/ml solutions in donepezil) in distilled water as vehicle, respectively.

3. Groupings and administration

Five rats per group (two groups) were used in this study as follows. The doses of test materials were selected based on theirtoxicity

Table 1. Composition of *Gongjindan* Used in This Study

Herbs	Scientific Names	Amounts (g/pill)
Antler (Cornuscerviparvum)	*Cervuselaphus*Linne	0.683
Angelicaegigantis radix	*Angelica gigas*Nakai	0.683
Ginseng steamed red	*Panax ginseng* CA Mey.	0.683
Cornifructus	*Cornusofficinalis*Sieb. Et Zucc	0.683
Rehmanniae radix preparata	*Rehmanniaglutinosa* (Gaertner) Liboschitz	0.683
Musk	*Moschusmoschiferus*Linne	0.122
Honey	*Apisindica*Radoszkowski	2.506
Gold plate		0.006
Total	8 types	6.050

Gongjindan used in this study was purchased from Daegu Oriental Hospital of DaeguHanny University (Daegu, Korea)

and pharmacodynamics - 10mg/kg of donepezil with 100mg/kg of *Gongjindan*. After 10mg/kg of donepezil treatment, *Gongjindan* 100mg/kg was administered, within 5 min. In donepezil single treated rats, 10mg/kg of donepezil was orally administered and 5 min after treatment, only distilled water 5ml/kg was orally administered, instead of *Gongjindan* suspensions. Each donepezil or *Gongjindan* was single orally administered, in a volume of 5ml/kg, dissolved in distilled water.

4. Plasma collections

All rats were slightly anesthesia under ethyl ether (Duksan Pure Chemical, Seoul, Korea) and blood samples (0.5 ml) were collected into 50IU heparinized tubes via the orbital plexus at 30min before treatment (as a control), 30min, 1, 2, 3, 4, 6, 8 and 24hrs after end of oral administration. Blood samples were immediately centrifuged for 10 min at 13,000 rpm and about 0.3ml aliquots of plasma were stored in a −70℃ deep freezer until analysis of donepezil.

5. Sample preparation and calibrations

Primary stock solution, 1.0mg/ml of donepezil in acetonitrile (Sigma, MO, USA) and internal standard working solution, carbamazepine (Sigma, MO, USA) 500ng/ml in acetonitrile were prepared. Working standard solutions were prepared by dilution with acetonitrile. All standard solutions were stored at -20℃ in the dark when not in use, and calibrated the standard samples as 100μl of blank plasma, working standard solutions and internal standard working solution were mixed with 100μl of acetonitrile. The mixtures were mixed by vortex-mixing and centrifuged at 12,000rpm for 10min at 4℃. The clear supernatants were transferred to injection vials and the aliquot was injected into the LC-MS/MS system. In addition, 100μl of sample plasma and internal standard working solution were mixed with 200μl of acetonitrile. The mixtures were mixed by vortex-mixing

and centrifuged at 12,000rpm for 10min at 4℃. Clear supernatants (3.5μl) were directly transferred to injection vials and the aliquot was injected into the LC-MS/MS system.

6. LC-MS/MS conditions

Concentrations of donepezilin the rat plasma samples were determined LC-MS/MS method. Chromatographic analysis was performed using an Agilent 1100 Series HPLC (Agilent Tech- nologies, CA, USA) equipped with on-line degasser, binary pump, autosampler and column compartment. Separation of the analyte from potentially interfering material was achieved at ambient temperature using Waters Xterra MS C18 columns (2.1×50mm, 3.5μm) (Waters Corp., MA, USA) at column oven 30℃. The mobile phase used for the chromatographic separation was composed of 2% acetonitrile/98% distilled water (0.1% formic acid) to 98% acetonitrile/2% distilled water (0.1% formic acid), and was delivered isocratically at a flow rate of 0.35ml/min. The column effluent was monitored using an API 2000 triple-quadruple mass-spectometric detector (Applied Biosystems, CA, USA). The instrument was equipped with an electrospray interface in positive ion mode, and controlled by the Analyst version 1.4.2 software (Applied Biosystems, CA, USA). Samples were introduced to the interface through a Turbo IonSpray with the temperature set at 400℃. A high positive voltage of 5.0kV was applied to the ion spray. Nitrogen was used as the nebulizer gas, curtain gas, and collision gas with the settings of 12, 6, and 8, respectively. The multiple reaction monitoring (MRM) detection method was employed for the detection of donepezil ; the transitions monitored were carbamazepine (IS): m/z 237>194 (Retention time: 2.4 min), donepezil: 380>91 (Retention time: 2.3 min). Calibration curves of donepezil were linear over the ranges studied with r^2> 0.999. The lower limit of quantification of the donepezil in the rat plasma was 1ng/ml.

7. Pharmacokinetic analysis

The plasma concentration data were analyzed using a noncompartmental method on commercial pharmacokinetics data analyzer programs (PK solutions 2.0; Summit, CO, USA)[28, 29]. The eliminationrate constant (K_{el}) was calculated by the log-linear regression of donepezil concentration data during the elimination phase, and the terminal half-life($t_{1/2}$) was calculated by 0.693/K_{el}. The peak concentration (Cmax) and time to reach the peak concentration(Tmax) of donepezil in the plasma were obtained by visual inspection of the data in the concentration-time curve. The area under the plasma concentration-time curve (AUC_{0-t}) from time zero to the time of the last measured concentration (C_{last})was calculated using the linear trapezoidal rule[30]. The AUCzero to infinity(AUC_{0-inf}) was obtained by adding AUC_{0-t} andthe extrapolated area was determined by C_{last}/K_{el}. The mean residencetime infinity (MRT_{inf}) was calculated by dividing the first moment of AUC($AUMC_{0-inf}$) by AUC_{0-inf}.

8. Statistical analyses

All the means are presented with their standard deviation of five rats (Mean ± SD of

five rat plasma concentrations of donepezil). The pharmacokinetic parameters were compared using a non-parametric comparison test, Mann-Whitney U (MW) test, on the SPSS for Windows (Release 14.0K, SPSS Inc., USA). A p-value <0.05 was considered statistically significant. In addition, the percent changes between donepezil single treated rats and donepezil with *Gongjindan* co-administered rats were calculated to help the understanding of the effects of co-administration.

III. Results

1. Changes on the plasma concentrations of donepezil

Donepezil was detected from 30min to 8hrs after end of administration in the both donepezil single and co-administered rats with *Gongjindan*, respectively. *Gongjindan* significantly ($p<0.01$) inhibited the absorption of donepezil at 2hrs after co-administration of donepezil 10mg/kg and *Gongjindan* 100mg/kg as compared with donepezil single treated rats, and the absorption of donepezil were also non-significant but markedly decreased at 30 min, 1, 3, 4, 6 and 8hrs after co-administration comparing with donepezil single treated rats (Fig 1).

The plasma donepezil concentrations at 30min, 1, 2, 3, 4, 6 and 8hrs after end of treatment were changed as -15.71, -30.25, -28.84, -24.63, -37.96, -17.80 and -19.40% in donepezil + *Gongjindan* treated rats as compared with donepezil single treated rats, respectively.

2. Changes on the Tmax of donepezil

The Tmax of donepezil were slightly and non-significantly decreased as -12.50% in co-administrated rats with donepezil 10mg/kg and *Gongjindan* 100mg/kg (0.70±0.27hr) as compared with donepezil single treated rats (0.80±0.27hr)(Table 2).

3. Changes on the Cmax of donepezil

The Cmax of donepezil were significantly ($p<0.05$) decreased as -27.76% in co-administrated rats with donepezil 10mg/kg and *Gongjindan* 100mg/kg (81.80±10.81ng) as compared with donepezil single treated rats (113.24±2.41ng) (Table 2).

4. Changes on the AUC of donepezil

The AUC_{0-t} of donepezil were significantly ($p<0.05$) decreased as -27.22% in co-administrated rats with donepezil 10mg/kg and *Gongjindan* 100mg/kg (264.19±42.09hr · ng/ml) as compared with donepezil single treated rats (362.99±90.04hr · ng/ml). In addition, AUC_{0-inf} of donepezil were also significantly ($p<0.05$) decreased as -26.54% in co-administrated rats with donepezil 10mg/kg and *Gongjindan* 100mg/kg (279.33±41.56hr · ng/ml) as compared with donepezil single treated rats (380.23±93.14hr · ng/ml)(Table 2).

5. Changes on the $t_{1/2}$ of donepezil

The $t_{1/2}$ of donepezil were slightly and non-significantly increased as 8.79% in co-administrated rats with donepezil 10mg/kg and

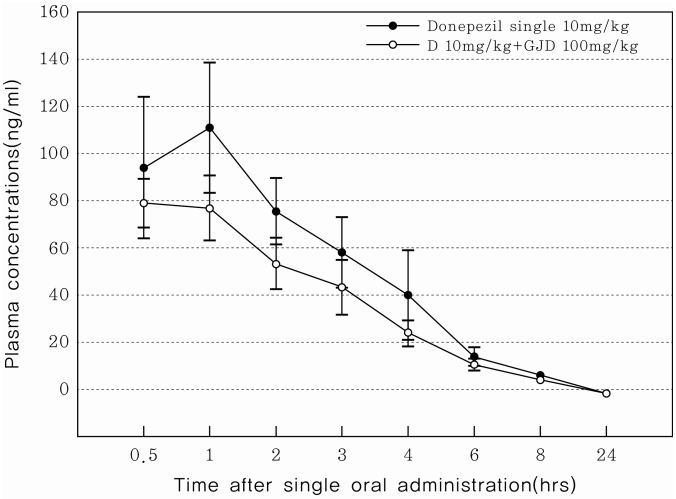

Fig 1. Plasma Concentrations of Donepezil with and without Gongjindan Co-administration in Male Rats. Donepezil was detected from 30min to 8hrs after end of administration in the both donepezil single and co-administered rats with *Gongjindan*, respectively. *Gongjindan* significantly ($p<0.01$) inhibited the absorption of donepezil at 2hrs after co-administration of donepezil 10mg/kg and *Gongjindan* 100mg/kg as compared with donepezil single treated rats, and the absorption of donepezil were also non-significant but markedly decreased at 30min, 1, 3, 4, 6 and 8hrs after co-administration as compared with donepezil single treated rats, in the present study. Values are expressed as mean ± SD of five rats (ng/ml). D, donepezil; GJD, *Gongjindan*.* $p<0.05$ as compared with donepezil single treated rats by MW test

Table 2. Pharmacokinetic Parameters of Donepezil with and without *Gongjindan* Co-administration in Male Rats

Parameters	Donepezil (10mg/kg)	
	Without *Gongjindan* co-administration(Distillwater)	With *Gongjindan* co-administration(100mg/kg)
Tmax (hrs)	0.80 ± 0.27	0.70 ± 0.27
Cmax (ng/ml)	113.24 ± 25.99	81.80 ± 10.81*
AUC_{0-t}(hr · ng/ml)	362.99 ± 90.04	264.19 ± 42.09*
AUC_{0-inf}(hr · ng/ml)	380.23 ± 93.14	279.33 ± 41.56*
$t_{1/2}$(hr)	1.65 ± 0.13	1.80 ± 0.21
MRT_{inf}(hr)	2.87 ± 0.06	2.96 ± 0.21

Values are expressed as mean ± SD of five rats. Cmax: The peak plasma concentration; Tmax: Time to reach Cmax; AUC_{0-t}: The total area under the plasma concentration-time curve from time zero to time measured; AUC_{0-inf}: The total area under the plasma concentration-time curve from time zero to time infinity; $t_{1/2}$: half life; MRT_{inf}: mean residence to time infinity. * $p<0.05$ as compared with donepezil single treated rats by MW test

Gongjindan 100mg/kg (1.80±0.21hr) as compared with donepezil single treated rats (1.65±0.13hr) (Table 2).

6. Changes on the MRT_{inf} of donepezil

The MRT_{inf} of donepezil were non-significantly changed as 3.11% in co-administrated rats with donepezil 10mg/kg and *Gongjindan* 100mg/kg(2.96±0.21hr) as compared with donepezil single treated rats (2.87±0.06hr) (Table 2).

IV. Discussion

Although donepezil is a centrally acting reversible acetylcholinesterase inhibitor, frequently used for palliative treatment of mild to moderate Alzheimer's disease[1] and for symptomatic treatment of patients with mild, moderate and severe dementia of the Alzheimer's type[2, 3], it also showed severe toxicity in preclinical studies[9] and undesirable side effects in clinical use[10-13]. In addition, donepezil has been showed various drug-drug interactions[9, 15], but the interactions with herbal natural products have not been established except for some restricted single herb extracts or natural compounds[16-19]. *Gongjindan*, a traditional Korean polyherbal formula is one of the most famous tonic agents and the hypolipidemic and immune stimulatory[20, 21], anti-oxidative[22], anti-gliosis effects[23] and anti-dementia effects[24, 25] of *Gongjindan* are relatively well documented. In the present study, the effects of *Gongjindan* co-administration on the pharmacokinetics of donepezil after single oral administration were observed as a process of the comprehensive and integrative medicine, combination therapy of donepezil with *Gongjindan* to achieve synergic pharmacodynamics and reduce toxicity. After 10mg/kg of donepezil treatment, *Gongjindan* 100mg/kg was administered within 5 min. The plasma were collected at 30min before administration, 30min, 1, 2, 3, 4, 6, 8 and 24hrs after end of *Gongjindan* treatment, and plasma concentrations of donepezil were analyzed using LC-MS/MS methods. PK parameters of donepezil (Tmax, Cmax, AUC, $t_{1/2}$ and MRT_{inf}) were analysis as compared with donepezil single administered rats using noncompartmental pharmacokinetics data analyzer programs.

Gongjindan markedly inhibited the absorption of donepezil regardless of sample time, from 30min to 8hrs after end of co-administration as compared with donepezil single treated rats. Especially the absorption of donepezil were significantly ($p<0.05$) decreased at 2hrs after co-administration as compared with donepezil single treated rats, in the present study. Accordingly, the Cmax (-27.76%), AUC_{0-t} (-27.22%) and AUC_{0-inf} (-26.54%) of donepezil in co-administered rats were significantly ($p<0.05$) decreased as compared with donepezil single treated rats, respectively. These findings are considered as direct evidences that *Gongjindan* decreased oral bioavailability of donepezil as inhibited the absorptions, when they were co-administered.

Donepezil was well absorbed, with a relative oral bioavailability of 100%[31]. The rate and extent of absorption are not influenced by food intake or the time of administration[32]. Donepezil showed very high protein bindings, it showed approximately 96% protein bindings[33], mainly to albumins (about 75%) and α1-acid

glycoprotein (about 21%). Tmax of donepezil in human subject after oral administration is 3 to 4 hours and slowly eliminated through renal and biliary system[34], $t_{1/2}$ of donepezil in healthy human volunteers is about 70 hours[35, 36]. In rats, Tmax of donepezil is 0.5~1hr after single oral administration and $t_{1/2}$ is about 2~3hrs[37]. In the present study, Tmax of donepezil in donepezil single oral treated rats was detected as 0.80±0.27hr, and Cmax, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$ and MRT_{inf} were detected as 13.24±25.99ng, 362.99±90.04hr · ng/ml, 380.23±93.14hr · ng/ml, 1.65±0.13hr and 2.87±0.06hr, respectively. In donepezil with *Gongjindan* co-administered rats, Tmax, Cmax, AUC_{0-t}, AUC_{0-inf}, $t_{1/2}$ and MRT_{inf} of donepezil were detected as 0.70±0.27hr, 81.80±20.81ng, 264.19±42.09hr · ng/ml, 279.33± 41.56hr · ng/ml, 1.80±0.21hr and 2.96±0.21hr; changed as -12.50, -27.76, -27.22, -26.54, 8.79 and 3.11% as compared with donepezil 10mg/kg single oral treated rats, respectively, in the present study. Especially, the Cmax, AUC_{0-t} and AUC_{0-inf} of donepezil in donepezil with *Gongjindan* co-administered rats were significantly ($p<0.05$) decreased as compared with donepezil single treated rats, respectively.

Donepezil undergoes first pass metabolism to four major metabolites, two of which are known to be active, and a number of minor metabolites[34]. Donepezil is metabolized by cytochrome P450 isoenzymes CYP2D6 and CYP3A4[34, 38]; and, therefore, donepezil can be interacted with other drugs act on these isoenzymes[9, 15]. As co-administration of *Gongjindan*, the absorption of donepezil was dramatically decreased in the present study. It, therefore, considered that co-administration with *Gongjindan* can be reduced the toxicity or side effects of donepezil[10-13] because toxicity or side effects of donepezil were directly related to the plasma concentrations. However, it also obvious evidences that the reduction of donepezil absorptions induced the decreases of pharmacodynamics. More detail pharmacokinetic studies should be tested to select optimal dosing regimens and to observe the possibilities that can be used as comprehensive and integrative therapy with *Gongjindan* and donepezil for dementia, when they were co-administered, like the effects after co-administration with reasonable intervals considering the Tmax of donepezil (about 1.5hr-intervals, in my opinion) and after repeated co-administrations.

V. Conclusions

Based on the results of the present study, co-administration of *Gongjindan* decreases the oral bioavailability of donepezil as inhibited the absorption. Hence, concomitant uses of *Gongjindan* with donepezil may require close monitoring for potential drug interactions. It, therefore, is considered that the more detail pharmacokinetic studies should be tested to conclude the effects of *Gongjindan* on the pharmacokinetics of donepezil, when they were co-administered, like the effects after co-administration with reasonable intervals considering the Tmax of donepezil (about 1.5hr-intervals) and after repeated co-administrations.

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